IJPAR |Volume 2 | Issue 1 | Jan -Mar- 2013 ISSN: 2320-2831

INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

Available Online at: www.ijpar.com

[Research article]

Synthesis, characterization of certain new heterocyclic hybrids of pyrazoles and evaluation of their anti-inflammatory activity

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ABSTRACT

The work presented in this article consists of synthesis, characterization and biological evaluation of substituted pyrazole derivatives. Pyrazole derivatives have been shown to have wide variety of pharmacological activities like anti-inflammatory, antidepressant and anticonvulsant. As combination of biologically active moieties into one molecule and synthesis of totally newer moieties have been the methods of research, the present study is an attempt to synthesize some novel pyrazole derivatives, incorporating various biologically active aryl / aryloxy acid derivatives, such as ibuprofen, diclofenac, aceclofenac as well as potent antibacterial quinolones, norfloxacin and ciprofloxacin. All the compounds synthesized were evaluated for their anti-inflammatory (Carrageenan induced paw oedema method) activity. The results obtained were found to be compatible with standard literature and standard drug employed. Hence, the obtained derivatives can be subjected to further clinical studies to optimize their clinical efficacy.

KEYWORDS: Pyrazoles, Anti-inflammatory, Quinolones derivatives

INTRODUCTION

During the last decade considerable interest has arisen in the field of anti-inflammatory agents. Inflammation although known in certain disease to affect the connective tissues of the joints, tendons, bones and heart, the etiology of the diseases and the mechanism is still eluding[1,2,3]. A number of anti-inflammatory agents have been discovered and many of them have disappeared from the market[4,5,6,7,8,9]. The reasons are mainly their side effects and lack of specificity. Moreover, the types of inflammation also vary and further the inflammations with regard to individuals also vary, which can be explained to some extent by the involvement of immunological factors in the medication of inflammation. All the anti-inflammatory agents discovered are not effective in all types of inflammation. However, it is very clear that till now, potent inhibitors of inflammation does not really exist and an intensive investigation seems to be definitely necessary.

In the forgoing survey of literature, it is seen that the drug design by molecular manipulation is a productive source of new drugs. Synthesis of compounds to explore the potential biologically active agents still draws continued interest. Pyrazole derivatives have been shown to have wide variety of pharmacological activities like anti-inflammatory[10], antidepressant[11], anticonvulsant[12]

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and anti-pyretic[13]. Molecular manipulation, combination of biologically active moieties into one molecule and synthesis of totally newer moieties have been the methods of approach. Hence, we present here synthesis of some novel pyrazole derivatives incorporating various biologically active aryl/aryloxy acid derivatives such as ibuprofen, diclofenac, aceclofenac as well as potent antibacterial quinolones, norfloxacin and ciprofloxacin.

MATERIALS AND METHOD

General method of preparation of hydrazide I (a-h)

The mixture of aryl/aryloxy acid (**R**) (0.1mol) and ethanol (50ml) were taken with a few drop of concentrated sulphuric acid and it was refluxed for 6 hours. The reaction mixture was concentrated by distilling off the excess of ethanol under reduced pressure and treated with a saturated solution of sodium bicarbonate. The ester obtained was used for the preparation of hydrazides directly. The ester (0.1 mole) was dissolved in appropriate quantity of ethanol and to this hydrazine hydrate (0.1 mole) was added. The reaction mixture was taken in a round bottomed flask and refluxed for a period of 12-18 hours. Excess of ethanol was distilled off under reduced pressure. It was then poured into ice cold water and the solid obtained was filtered. It was recrystallised from suitable solvent.

The following hydrazides were prepared.

1. 2-hydroxy-1-benzenecarbohydrazide
2. 2-phenylethanohydrazide
3. 2-Pheoxyethano hydrazide
4. 2-(4-isobutylphenyl)propanohydrazide
5. 1-ethyl-6-fluoro-4-oxo-7-piperazino-1,4-dihydro -3-quinoline carbohydrazide
6. 2- [2-(3,5-dichloroanilino) phenyl] ethano hydrazide
7. 2-hydrazino-2-oxoethyl2-[2-(2,6-dichloroanilino) phenyl] acetate
8. 1-cyclopropyl-6-fluoro-4-oxo-7-piperazino-1,4-dihydro-3-quinolinecarbohydrazide.

Preparation of 3, 5-dimethyl-1*H*-1-substituted pyrazoles II (a-h)

The equimolar quantities of hydrazides I (a-h) and acetyl acetone was refluxed in methanol (25ml) containing few drops of concentrated HCl for 5-6 hours on water bath. The reaction mixture was cooled to room temperature and the solid separated was filtered, washed with petroleum ether, dried and recrystallized from suitable solvent.

EXPERMENTAL WORK

Pyrazoles derivatives are synthesized as shown in the scheme in figure 1. Melting Points were determined by using Toshniwal apparatus in open capillaries and are corrected. The purity of the compounds were checked by TLC on silica gel G plates using n-butanol, ethyl acetate (1:3) solvent system and UV lamp was used as a visualizing agent. IR spectra were recorded using KBr pellets on a Jasco FT/IR 5300 series spectrophotometer. ^{1}H NMR Spectra on an Avance 300MHZ spectrophotometer using DMSO d_6 as solvents and TMS as internal standard (chemical shift values are expressed in δ ppm). Mass Spectra were recorded by LCMS technique on a liquid chromatography mass spectrophotometer.

Figure: 1 Synthetic scheme of pyrazoles derivatives.

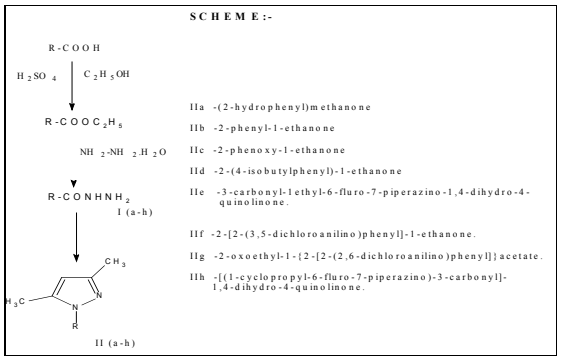


TABLE 1: Physical characteristic data of intermediates I(a-h)

Sr.No	Compound code	R	Molecular Formula	Mol. Wt.	Melting point	Yield %
1	Ia	Salicyclic acid	$C_{17}H_8N_20_2$	152.152	^{0}178 C	70
2	Ib	Phenyl acetic acid	$C_8H_{10}N_20$	150.179	^{0}121 C	73
3	Ic	Phenoxy acetic acid	$C_8H_{10}N_20_2$	166.178	^{0}110 C	74
4	Id	2(4-isobutyl phenyl)Propionic acid	$C_{13}H_{20}N_20$	220.313	^{0}72 C	68
5	Ie	1-Ethyl-6-fluro-1,4dihydro-4-oxo-7-(1-piperazinyl)-3-	$C_{16}H_{22}FN_50_2$	335.380	^{0}222 C	65
6	If	[o-(2,6-dichloroanilino)phenyl]acetate	$C_{14}H_{13}Cl_2N_30$	310.182	^{0}104 C	60
7	Ig	2-({2-[(2,6-dichloroanilino)phenyl]acetyl}-oxy)acetic acid	$C_{16}H_{15}Cl_2N_30_3$	368.218	^{0}145 C	76
8	Ih	1-cyclopropyl-6-fluro-1,4dihydro-4-oxo-7-(1-piprazinyl)-3-quinolinecarboxylic acid	$C_{17}H_{22}FN_50_2$	347.391	^{0}265 C	70

TABLE 2: Physical characteristic data of synthesized compounds II (a-h)

Sr. No.	Compound Code	R	Molecular Formula	Mol. wt	Melting point	Yield %	Rf
1	IIa	-(2-hydrophenyl)methanone	$C_{12}H_{12}N_20_2$	216.238	$_{154}{}^0$C	75	0.51
2	IIb	-2-phenyl-1-ethanone	$C_{13}H_{14}N_20$	214.268	$_{227}{}^0$C	72	0.63
3	IIc	-2-phenoxy-1-ethanone	$C_{13}H_{14}N_20_2$	230.265	$_{135}{}^0$C	67	0.58
4	IId	-2-(4-isobutylphenyl)-1-ethanone	$C_{17}H_{22}N_20$	270.373	$_{220}{}^0$C	77	0.49
5	IIe	-3-carbonyl-1ethyl-6-fluro-7-piperazino-1,4-dihydro-4-quinolinone.	$C_{21}H_{24}FN_50_2$	397.451	$_{245}{}^0$C	80	0.53
6	IIf	-2-[2-(3,5-dichloroanilino)phenyl]-1-ethanone.	$C_{19}H_{17}Cl_2N_30$	374.268	$_{177}{}^0$C	70	0.51
7	IIg	-2-oxoethyl-1-{2-[2-(2,6-dichloroanilino) phenyl]}acetate.	$C_{21}H_{19}Cl_2N_30_3$	432.304	$_{145}{}^0$C	74	0.76
8	IIh	-[(1-cyclopropyl-6-fluro-7-piperazino)-3-carbonyl]-1,4-dihydro-4-quinolinone.	$C_{22}H_{24}FN_50_2$	409.462	$_{269}{}^0$C	72	0.47

ANTI-INFLAMMATORY ACTIVITY

All the synthesized compounds were evaluated for their anti-inflammatory activity using Carrageenan induced rat hind paw oedema method at two dose levels, 50mg/kg (low dose) and 100mg/kg (high dose). The reduction in paw oedema volume was measured in mm using plethysmograph and the percent reduction in edema volume was determined comparing with control. The anti-inflammatory drug Ibuprofen was used as reference standard.

RESULT AND DISCUSSION

Spectral Data

IIb- Aromatic C-H was absorbed in the form of intense peak at 3100 cm^{-1}, Aliphatic C-H peaks are also obtained from 3032 cm^{-1} to 2843 cm^{-1}. The C=O absorption peak was seen at 1607 cm^{-1}. The ^{1}HNMR spectrum recorded in DMSO D_6 exhibited two identical peaks in the form of singlet at 2.3δ and CH_2 protons absorption has merged with DMSO protons at 3.5δ.

The methyl proton and aromatic together have shown multiplet from 7.1δ to 8.3δ. The base peak is observed by Mass spectra is m/z 91.

SPECTRAS

Fig. No. 2 I.R. of Compound IIb

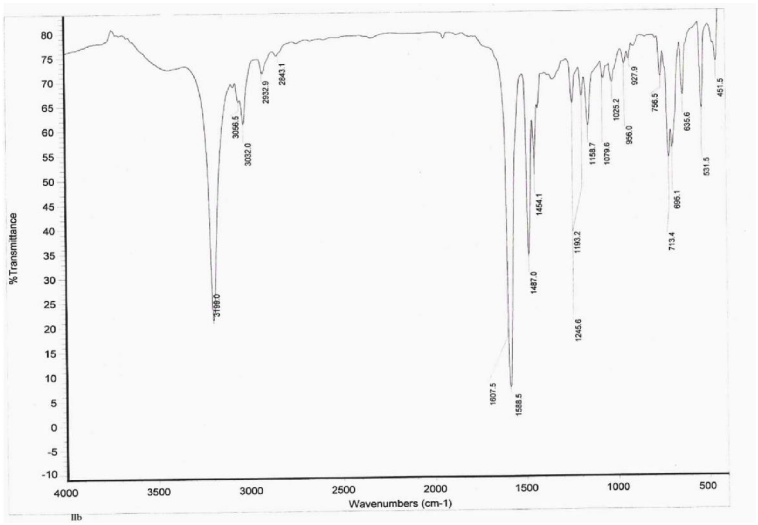


Fig. No.3 NMR. Of Compound IIb

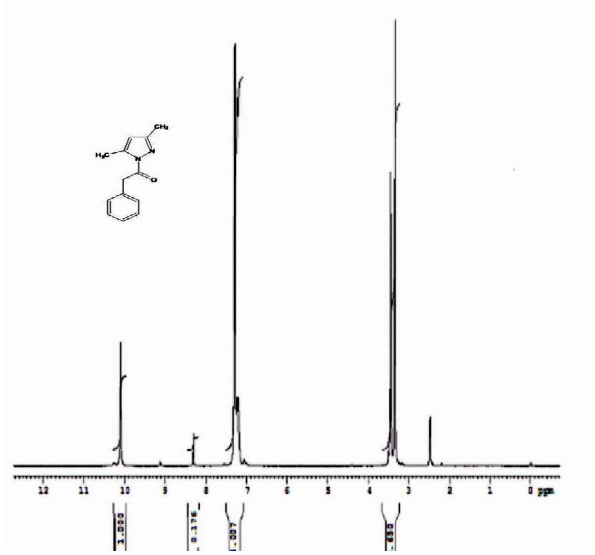


Fig. No. 4 NMR. Of Compound IIb

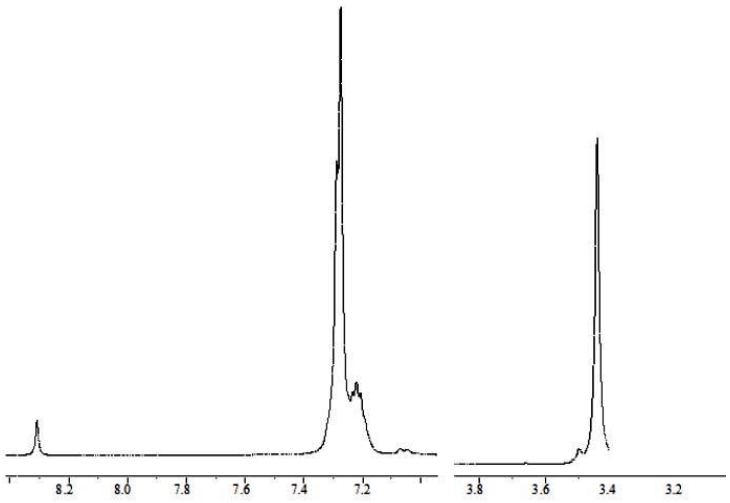
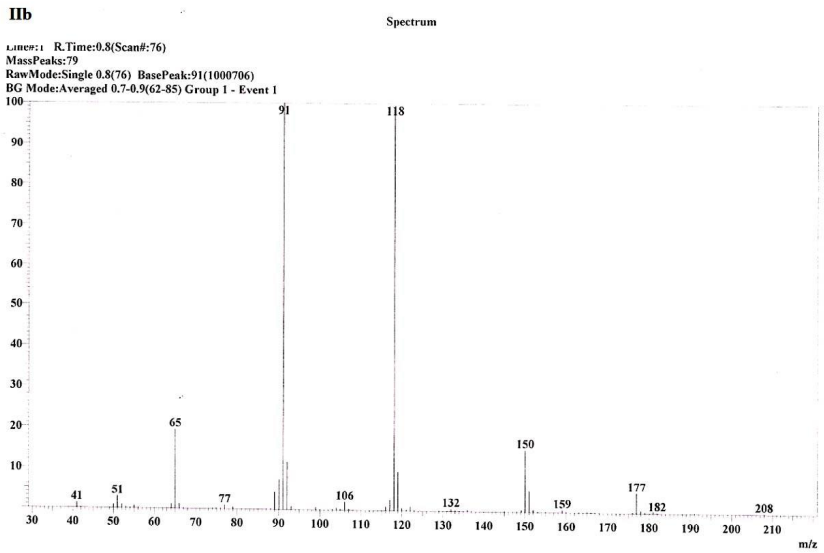


Fig. No. 5 MASS of Compound IIb



IIf-The N-H group present in the molecule sandwich between two phenyl molecules, exhibited a sharp peak at 3323 cm^{-1}, the aromatic and aliphatic C-H have exhibited an absorbance peak from 2854 cm^{-1} to 3078 cm^{-1}. The C=O group present in the molecule in the form of imine exhibited a peak at 1694 cm^{-1}. The ^{1}HNMR spectra of these molecules exhibits a broad peak at 3.3δ due to the presence of two CH_3 protons present in the molecule. The aromatic protons present in the molecule exhibited aromatic cluster from 6.8δ to 7.3δ in the form of a multiplet. The C-H peak of methylene appears to have merged with the aromatic cluster and the methylene protons sandwich between carbonyl group as well as phenyl moiety have been desheilded and gave a peak at 6.8δ. The H of N-H protons was resonated at 7.1δ. These measurement recorded are in concerns with proposed structure of the molecules. The base peak is observed by Mass spectra is m/z 214.

Fig. No. 6 I.R. Of Compound IIf

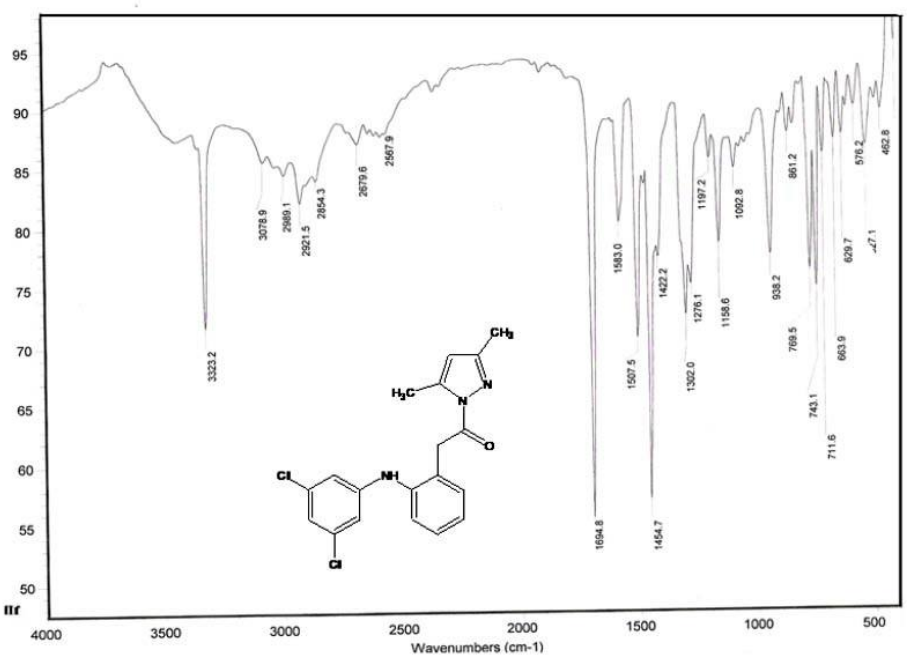


Fig. No. 7 N.M.R. Of Compound IIf

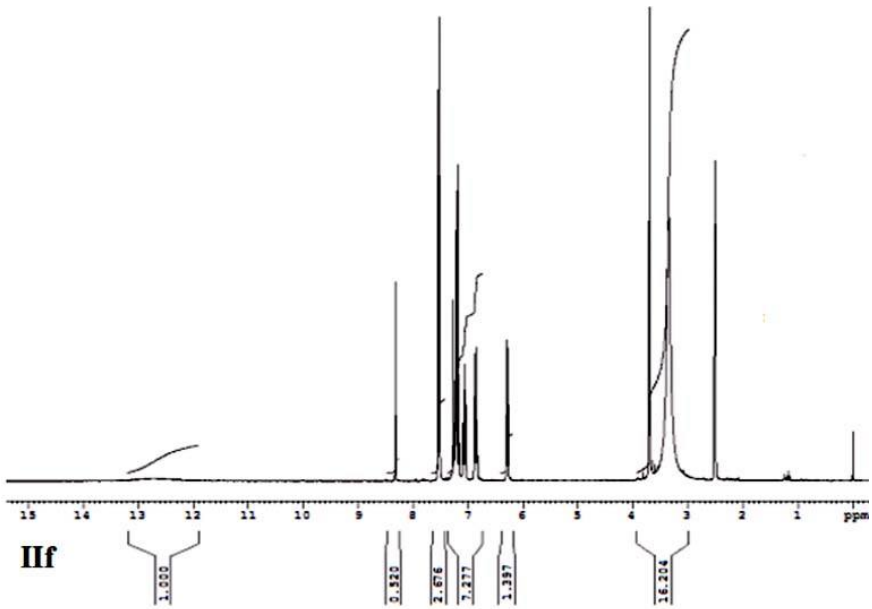


Fig. No. 8 N.M.R. Of Compound IIf

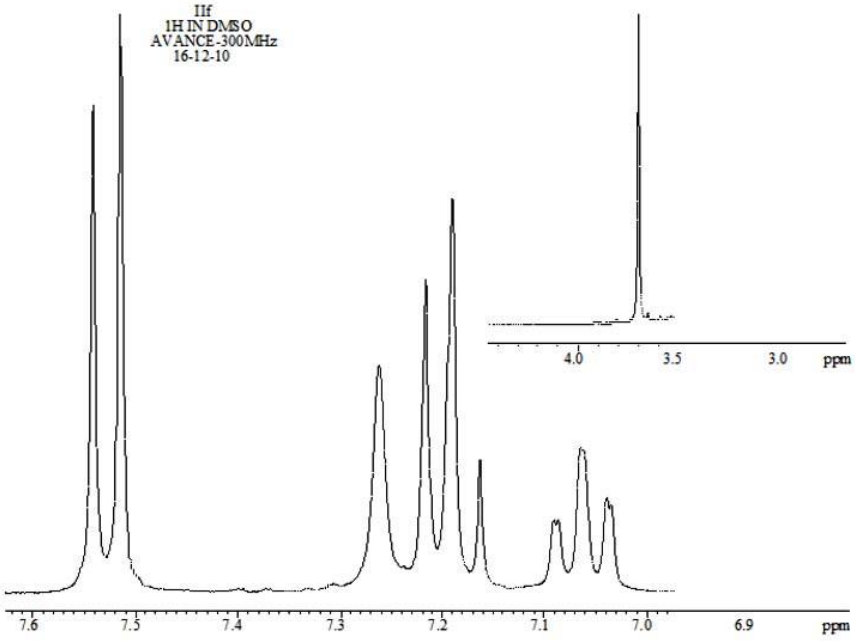


Fig. No. 9 MASS of Compound IIf

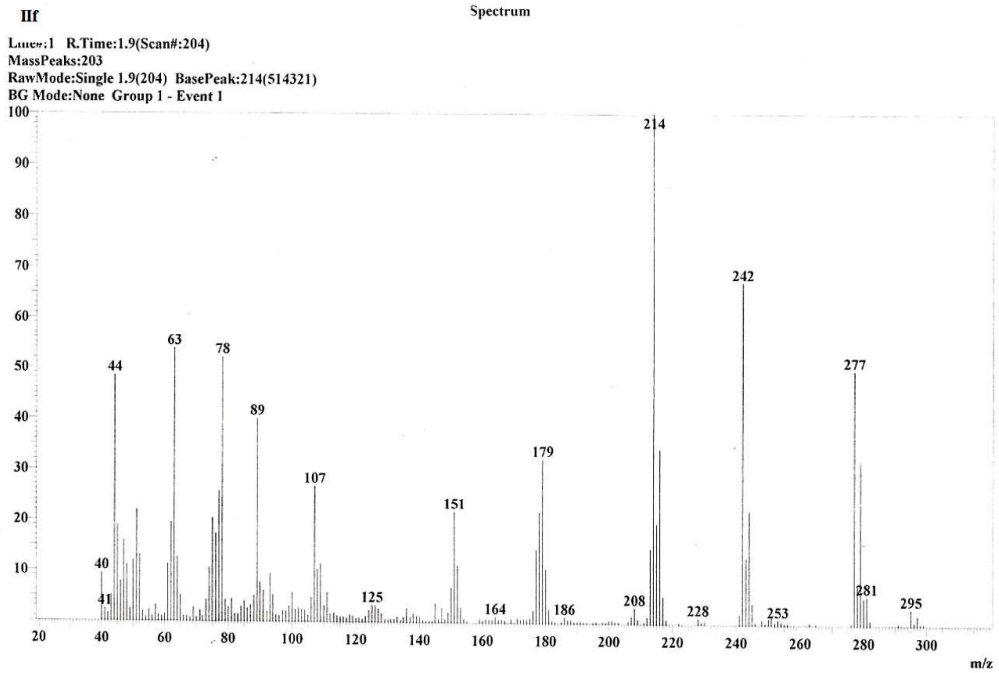
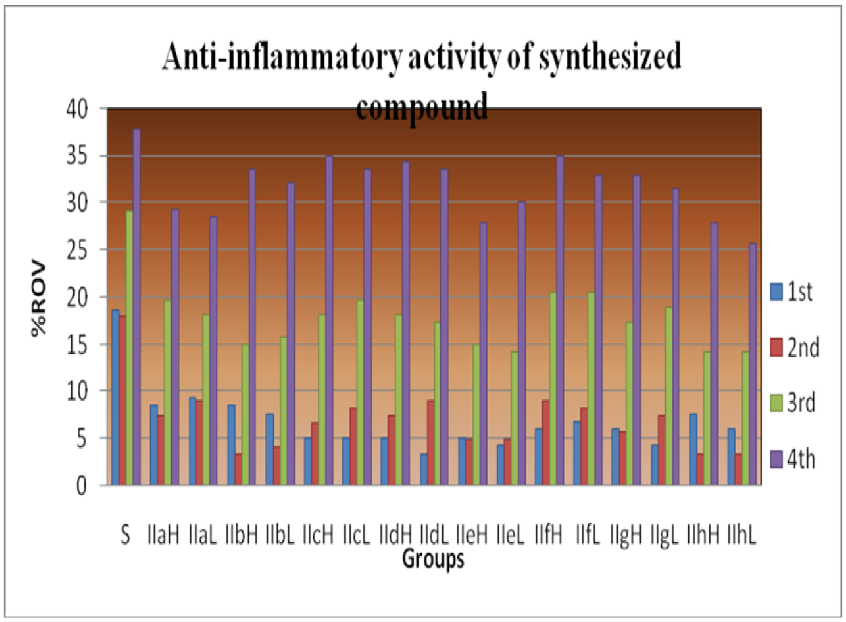


TABLE 3: Anti-inflammatory activity of newly synthesized Pyrazole derivatives.

Group	Treatment	Dose Mg/kg	Paw Oedema volume After 1st hr		After 2nd hr		After 3rd hr		After 4th hr	
			Mean	%ROV	Mean	%ROV	Mean	%ROV	Mean	%ROV
	Control	0.5ml	1.18±0.005		1.22±0.002		1.27±0.001		1.4±0.0057	
	Standard Ibuprofen	100	0.96±0.005***	18.64	1±0.001***	18.03	0.9±0.002***	29.13	0.87±0.005***	37.85
1	IIa H	100	1.28±0.002*	8.47	1.13±0.003*	7.37	1.02±0.002***	19.68	0.99±0.005***	29.28
	IIa L	50	1.29±0.001**	9.32	1.11±0.006**	9.01	1.04±0.002***	18.11	1±0.003***	28.57
2	IIb H	100	1.28±0.004*	8.47	1.18±0.005n.s	3.27	1.08±0.003***	14.96	0.93±0.004***	33.57
	IIb L	50	1.27±0.004*	7.62	1.17±0.003*	4.09	1.07±0.005***	15.74	0.95±0.005***	32.14
3	IIc H	100	1.24±0.002*	5.08	1.14±0.001*	6.55	1.04±0.004***	18.11	0.91±0.002***	35
	IIc L	50	1.24±0.001*	5.08	1.12±0.002**	8.19	1.02±0.001***	19.68	0.93±0.003***	33.57
4	IId H	100	1.24±0.002n.s	3.38	1.13±0.003*	7.37	1.04±0.005***	18.11	0.92±0.002***	34.28
	IId L	50	1.22±0.002*	5.03	1.11±0.003**	9.01	1.05±0.005***	17.32	0.93±0.002***	33.27
5	IIe H	100	1.24±0.005n.s	4.23	1.16±0.005*	4.91	1.08±0.004***	14.96	1.01±0.006***	27.85
	IIe L	50	1.23±0.006*	5.96	1.16±0.006*	4.91	1.09±0.001***	14.17	0.98±0.004***	30
6	IIf H	100	1.25±0.002*	5.96	1.11±0.007**	9.01	1.01±0.003***	20.47	0.91±0.005***	35
	IIf L	50	1.26±0.003*	6.77	1.12±0.006**	8.91	1.01±0.003***	20.47	0.94±0.004***	32.85
7	IIg H	100	1.25±0.004*	5.93	1.15±0.007*	5.73	1.05±0.004***	17.32	0.94±0.002***	32.85
	IIg L	50	1.23±0.004*	4.23	1.13±0.006*	7.37	1.03±0.006***	18.69	0.96±0.002***	31.42
8	IIh H	100	1.22±0.003*	7.62	1.18±0.004n.s	3.27	1.09±0.001***	14.17	1.01±0.003***	27.85
	IIh L	50	1.25±0.002*	5.93	1.18±0.004n.s	3.27	1.09±0.002***	14.17	1.04±0.005***	25.71

Figure 10- Anti-inflammatory activity of newly synthesized Pyrazole derivatives.



CONCLUSION

During the present investigation, the new pyrazole derivatives have been successfully synthesized by linking two biologically active moieties, such as anti- inflammatory molecules, Ibuprofen, Diclofenac, Acelofenac and synthetic antibacterial agents like Ciprofloxacin and Norfloxacin with pyrazole moiety. This was done based on the observation that combination of biologically active moieties into one molecule and synthesis of totally newer moieties may result into compounds with improved potency and reduced toxicity. Even though the results obtained reveals that, few of the synthesized pyrazole derivatives are inferior to that of the standard drugs employed, while few of the compounds displayed encouraging results and were found to possess good anti-inflammatory activity. All the above results establish the fact that, the obtained pyrazole moiety can be a rich source for further exploitation. Hence, in search for new generation of drugs with high potency, selectively and reduced toxicity, it may be worthwhile to explore the possibility in this area by fusing different moieties. If suitably exploited it may results in better compounds.

ACKNOWLEDGEMENT

The authors are thankful to Management of Luqman College of Pharmacy, Gulbarga, for providing necessary research facility to carry out the research work. The authors also wish to thank Management of K T Patil College of Pharmacy, Osmanabad and KCT College of Pharmacy Gulbarga, for their constant encouragement and support.

REFERENCES

[1] Smith SE. Inflammation (ED) Vane JR, Ferriera SH.Springer Verlag Borlin Heidelberg, New York 1978.
[2] Bainton DF. The vell biology of inflammation. Gerald Welssmann (ED).
[3] Zoigler EI, Lohrbuch de pathologischen. Anatomic 6th edtion 1889.
[4] Glen H, Hamor. Principle of Med.Chemistry 2nd Edition p.563.
[5] Corletti A, Berde B, Newbold K, Taeschler M.Bull.Chem.Farm 1963,102,602.
[6] White house MW.prog.Drug Reasearch 1965.8,321.
[7] Packman MA, Nishizawa EE, Mustard JF. Biochem. Pharmacol. Suppl.1968,171-184.
[8] Shen TY. International symposium on NSAID. Garattini and MNG.Dukes (Edn) Excerpta. Medica.1964; NYP 232.
[9] Carson JR, Mekivestry DN, Wong S. J.Med. Chem 1961;14,646.
[10] Tewari A K, Mishra A. Synthesis and anti-inflammatory activity of N^4, N^5 – Disubstituted-3-methyl - 1H - pyrazolo[3,4-C]pyridazine's. Bioorganic and medicinal chemistry 2001; 9(3):715-718.
[11] Mohammed Abdel-Aziz, Gamal El-Din A.Abou-Rahma, Alaa A Hassan. Synthesis of novel pyrazole derivatives and evaluation of their anti-depressant and anti-convulsant activities. European journal of Medicinal Chemistry 2009: 44:3480-3487.
[12] Michon V, Penhoat C Herve Du, Tombert F, Gillardin J M, Lepage F and Berthon L. Perparation, structural analysis and anti-convulsant activity of 3- and 5- aminopyrazole N- benzoyl derivatives. European journal of Medicinal Chemistry 1995; 30(2): 147-155
[13] El-Shimaa MN Abdel- Hafez, Gamal El-Din AA, Abuo-Rahma, Mohamed AA, Mohamed FR, Hassan HF. Design, synthesis and biological investigation of certain pyrazole-3-carboxylic acid derivatives as novel carriers for nitric acid. Bioorg and Med Chem 2009; 17: 3829-3837.
[14] Shivaji B, Tapas KS, Suvra M, Prabhash CD and Sridhar S. Ind J Pharmac 2000; 32: 21.
[15] Nivsarkar M, Mukherjee M, Patel M, Padh H and Bapu C. Indian Drugs 2002; 39(5): 290.

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